REMARKS

Reconsideration of this application and entry of this amendment are requested. Claims 8-12, 14, 19, 20 and 22-25 are active in the application subsequent to entry of this amendment. Claims 1-7,13, 15, 16 and 21 have been withdrawn.

It is proposed to amend the claims in order to more particularly point out and distinctly claim that which applicants regard as their invention and to reduce issues. More specifically, it is proposed to cancel claims 1-7, 13, 15, 16 and 21 and to amend claims 8-12, 14, 19 and 20. Previous claim 16 will be replaced with new claim 22 and new claims 23-25 added.

In the claim amendments proposed above, all of the independent claims specify the emulsion preconcentrate provides an average droplet size of from 2 to 10 microns as disclosed in the application at page 2 line 19. In addition, this emulsion preconcentrate, when mixed with an aqueous medium, upon oral administration provides an anticancer drug bioavailability ranging from 25% to 60% of that dose. This is based on the discussion found at page 9, lines 11-36 of the specification. New claim 22 is directed to a filled soft or hard gelatin capsule as disclosed in the specification at page 5, line 24. New claims 23 and 24 correspond to previous claims 6 and 7, respectively. The taxane materials defined in claim 25 find basis in the description of the invention at page 2, lines 13-15 and for Paclitaxel in the working examples. Accordingly, the new claims presented above are fairly based on the original disclosure and do not raise issues of new matter. Favorable consideration and entry of this amendment is requested.

The Official Action rejects claims 1-11 and 19 as allegedly being anticipated and all of previous claims 1-21 as being "obvious" over the disclosures of a single reference. To the extent the examiner's concerns may extend to the amended and new claims presented above, these rejections are respectfully traversed.

Hauer, et al. in US Patent 5,342,625 describe the cyclosporins as "a class of structurally distinctive, cyclic, poly-N-methylated endecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-

parasitic activity" (column 1, lines 11-15) with "potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis and, yet more recently, use as an agent for reversing or abrogating anti-neoplastic agent resistance in tumors and the like" (column 2, lines 15-18). Further, "many cyclosporins exhibit comparable pharmaceutical utility to Cyclosporin or more specific utility, for example activity particularly in reversing tumor resistance to cytostatic therapy ..." (column 3, lines 18-19). And further, cyclosporin has utility in "therapy in the treatment of autoimmune diseases and other conditions affecting the skin, for example for the treatment of atopic dermatitis and psoriasis and, as also widely proposed in the art, for hair growth stimulation, e.g. in the treatment of alopecia due to ageing or disease" (column 4, lines 51-55). It is taught by Hauer that cyclosporins may have "activity ... in reversing tumor resistance to cytostatic therapy" and "for reversing or abrogating anti-neoplastic agent resistance in tumours." However, cyclosporins are not taught by Hauer to be antitumor agents like the taxanes.

Although, cyclosporine has been proposed to be used in the treatment of cancer as an adjuvant for potentially reversing antineoplastic agent resistance in tumors, it is not considered an antineoplastic or cytotoxic agent as such.

It is however well established that majority of transplant patients receiving immunosuppressive agents like cyclosporine develop skin cancer including squamous cell and Kaposi's sarcoma (see Otley et al[1], Liver Transpl. 6(3):253-262, 2000). Recently, Hojo et al (Nature 397:530-534, 1999) reported that cyclosporine itself may have carcinogenic properties independent of its immunosuppressive effect.

Paclitaxel, in contrast, is a cytotoxic antineoplastic agent acting through its an anti-mitotic activity. Paclitaxel and taxanes in general bind and stabilize microtubules and thereby inhibit cell division.

Chemically cyclosporine and paclitaxel are very different. Cyclosporine is a cyclic peptide of 11 amino acids (see for example Bollinger et al, US Patent 4,384,996

"Novel cyclosporins") and containing amide bonds in the ring system while taxanes such as paclitaxel are complex diterpenoids (see for example Colin et al., US Patent 4,814,470, "Taxol derivatives, their preparation and pharmaceutical compositions containing them").

Comparison of properties of cyclosporin and paclitaxel are provided below.

Property	Cyclosporine	Paclitaxel
Melting point	150° C	213° C (decomp)
Empirical formula	$C_{62}H_{111}N_{11}O_{12}$	$C_{47}H_{51}NO_{14}$
Molecular weight	1,203 dalton	854 dalton
Solubility in methanol	Freely soluble	Crystallized from methanol

In view of the differences in chemical structure and properties between the two classes of unrelated molecules, it is not obvious to one skilled in the art to formulate taxanes such as paclitaxel according to Hauer et al's teaching for cyclosporins. The relatively large difference in the melting points of cyclosporin and paclitaxel suggest differences in their crystal lattice are to be expected, and therefore differences in their interaction with and affinities for various hydrophilic and lipophilic solvents are to be expected. Formulation approaches a person skilled in the art would take to make a microemulsion containing a member of one of the cyclosporin class of compounds are therefore expected to be different from formulation approaches that person skilled in the art would take to make microemulsions containing a member of the taxane class of compounds.

M.C. Martini in "Interet des vehicules microemulsionnes" Chapter 16, p. 412-440 in Formes Pharmaceutiques pour Application Locale, Edited by M. Seiller and M-C Martini, Tec Doc Publishers, Paris (1996) writes on pages 412-417 about formulations of microemulasion: "The formulation of pharmaceutical microemulsions is fastidious since

[1] These were published well after applicants' priority dates and thus not available as prior art

it is always dependent on subtle characteristics of the raw materials, which are often not present in regulated Pharmacopeia. It is equally dependent on the physico-chemical characteristics of the active principal ingredients that have to be incorporated [in the microemulsions]."

The microemulsion preconcentrates of Hauer et al. when added to water form microemulsions in water having an average particle size of less than 1,000 nanometers. However, the emulsion preconcentrates of the current invention form dispersions with droplets having average size of up to 10 microns. This is in the size range found in emulsions. While the emulsion preconcentrates of the current invention exit as microemulsions, it is not necessary for the preconcentrates of the current invention to form stable microemulsions when mixed with water to provide their increased bioavailability of the taxane in the preconcentrate. This in not taught by Hauer et al.

For the above reasons is is respectfully submitted that the claims of this application as above amended define inventive subject matter. Reconsideration, entry of this amendment and allowance are solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

8. (Amended) A storage-stable, self-emulsifying, non-aqueous, emulsion preconcentrate of a dose of an anticancer drug in a microemulsion consisting essentially of:

10 to 80% w/w of a hydrophobic component of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil or mixtures thereof; 20 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant,

0-35% w/w diethylene glycol monoethylether, and

0 to 40% w/w of at least one hydrophilic component selected from a hydroxyalkane, dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof ,

wherein said emulsion preconcentrate, when mixed with an aqueous medium, gives an average [particle] droplet size of [at most] 2 to 10 microns or which upon oral administration has anticancer drug bioavailability ranging from 25% to 60% of said dose.

9. The self-emulsifying emulsion preconcentrate of claim 8 containing from 15 to 75% w/w hydrophobic component.

10. The self-emulsifying emulsion preconcentrate of claim 8 containing from 20 to 80% w/w surfactant.

11. The self-emulsifying emulsion preconcentrate of claim 8 containing up to 30% w/w hydrophilic component.

12. (Amended) A storage-stable, self-emulsifying, non-aqueous clear, liquid emulsion preconcentrate of a dose of at least one taxane in a composition consisting essentially of:

10 to 80% w/w of a hydrophobic component of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil or mixtures thereof;

20 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant, and

up to 40% w/w of at least one hydrophilic component selected from a hydroxy alkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and 1,2-propylene glycol, ethanol or a mixture[s] thereof ,

wherein said emulsion preconcentrate, when mixed with an aqueous medium, disperses to form an emulsion having droplets of [gives an] average [particle] size of [at most] 2 to 10

microns, or which upon oral administration [forms *in situ* a microemulsion in the gastrointestinal tract] has taxane bioavailability ranging from 25% to 60% of said dose.

14. The liquid preconcentrate of claim [13] 12 wherein [the hydrophilic component is present and is a mixture of] 1,2-propylene glycol and ethanol are in combination.

17. An orally administrable pharmaceutical composition consisting essentially of the preconcentrate of claim 12 in a pharmaceutically acceptable carrier or diluent.

18. A parenterally injectable pharmaceutical composition consisting essentially of the preconcentrate of claim 12 in a pharmaceutically acceptable diluent.

19. (Amended) A method of orally or parenterally administering an anticancer drug to a subject in need of same comprising administering a storage-stable, self-emulsifying, non-aqueous, emulsion preconcentrate of a dose of an anticancer drug consisting essentially of:

10 to 80% w/w of a hydrophobic component of at least one triglyceride, diglyceride, monoglyceride, free fatty acid, fatty acid ester, fish oil, vegetable oil and mixtures thereof;

20 to 80% w/w of surfactant phase comprising at least one non-ionic surfactant, and

up to 40% w/w of at least one hydrophilic component selected from a hydroxy alkane, a dihydroxy alkane, a polyethylene glycol having an average molecular weight of at most 1000, and mixtures thereof,

wherein said emulsion preconcentrate, when mixed with an aqueous medium, gives an average [particle] droplet size of [at most] 2 to 10 microns or which upon oral administration has anticancer drug bioavailability ranging from 25% to 60% of said dose.

20. (Amended) A method of of claim [12] 19 wherein the anticancer drug is a taxane solubilized in the emulsion preconcentrate [stable, self-emulsifying system which self-disperses in water, simulated intestinal, or simulated gastric fluid to yield a homogeneous phase with a particle size of 10 microns].